

WHAT IS CLAIMED IS:

1. A sustained-release oral analgesic dosage form for once-a-day administration, comprising:  
a unit dose of a plurality of inert pharmaceutically acceptable substrates comprising an analgesically effective amount of an opioid analgesic or a salt thereof in sustained release form, each of said substrates having a diameter from about 0.1 mm to about 3 mm, said unit dose being bioavailable and providing effective blood levels of said opioid analgesic for at least about 24 hours.
2. The dosage form of claim 1, wherein said substrates are selected from the group consisting of spheroids, beads, microspheres, seeds, pellets, ion-exchange resin beads, granules, and mixtures thereof.
3. The dosage form of claim 2, wherein said substrates are inert beads coated with said opioid analgesic.
4. The dosage form of claim 2, wherein said substrates comprise matrices of a substantially uniform mixture of said opioid analgesic and a hydrophobic material.

5. The dosage form of claim 1, wherein said opioid analgesic is selected from the group consisting of morphine, codeine, hydromorphone, hydrocodone, oxycodone, oxymorphone, dihydrocodeine, dihydromorphone, and mixtures thereof.
6. The dosage form of claim 1, wherein said opioid analgesic is selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphone, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacyl morphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol,

properidine, propiram, propoxyphene, sufentanil, tramadol, tilidine, salts thereof and mixtures thereof.

7. The dosage form of claim 5, wherein said opioid analgesic consists of from about 2 mg to about 64 mg hydromorphone.
8. The dosage form of claim 5, wherein said opioid analgesic consists of from about 5 mg to about 800 mg morphine.
9. The dosage form of claim 1, wherein said opioid analgesic consists of from about 5 mg to about 400 mg oxycodone.
10. The dosage form of claim 1 which provides a peak plasma level of said opioid in-vivo from about 2 to about 10 hours after administration.

11. The dosage form of claim 1 which provides a peak plasma level of said opioid in-vivo from about 2 to about 4 hours after administration.
12. The dosage form of claim 3, wherein said hydrophobic material is selected from the group consisting of an acrylic polymer, an alkylcellulose, shellac, zein, hydrogenated vegetable oil, hydrogenated castor oil, and mixtures of any of the foregoing.
13. The dosage form of claim 12, wherein said hydrophobic material is applied to said plurality of said substrates as an aqueous dispersion.
14. The dosage form of claim 1, wherein said unit dose of said substrates are contained within a hard gelatin capsule.
15. The dosage form of claim 1, wherein each of said substrates having a diameter from about 0.5 mm to about 2 mm.
16. The dosage form of claim 3, wherein each of said beads is from about a 8 mesh bead to about 50 mesh bead.

17. The dosage form of claim 1, further comprising release-modifying agents, said release-modifying agents comprising one or more hydrophilic polymers such as hydroxypropylmethylcellulose.
18. A dosage form of claim 1, further comprising a non-opioid drug.
19. The dosage form of claim 18, wherein the said non-opioid drug is a non-steroidal anti-inflammatory agent.
20. The dosage form of claim 19, wherein said non-steroidal anti-inflammatory agent is selected from the group consisting of ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acetaminophen, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam or isoxicam, and mixtures of any of the foregoing.

21. A bioavailable sustained-release opioid analgesic dosage form for once-a-day oral administration, comprising
- inert pharmaceutically acceptable beads having a diameter from about 0.1 mm to about 3 mm coated with an analgesically effective amount of an opioid analgesic or a salt thereof, said beads further comprising an sustained-release overcoat comprising an effective amount of a hydrophobic material selected from the group consisting of an acrylic polymer, an alkylcellulose, shellac, zein, hydrogenated vegetable oil, hydrogenated castor oil, and mixtures of any of the foregoing to provide a sustained release of said opioid analgesic in aqueous solutions for at least about 24 hours.
22. The dosage form of claim 21, wherein said opioid analgesic consists of from about 2 mg to about 64 mg hydromorphone.
23. The dosage form of claim 21, wherein said opioid analgesic consists of from about 5 mg to about 800 mg morphine.

24. The dosage form of claim 21, wherein said opioid analgesic consists of from about 5 mg to about 400 mg oxycodone.
25. The dosage form of claim 21 which provides a peak plasma level of said opioid in-vivo from about 3 to about 10 hours after administration.
26. The dosage form of claim 21, wherein said unit dose of said beads are contained within a hard gelatin capsule.
27. The dosage form of claim 21, wherein each of said beads having a diameter from about 0.5 to about 2 mm.
28. The dosage form of claim 21, wherein each of said beads is from about 8 mesh to about 50 mesh.
29. The dosage form of claim 21, wherein said opioid analgesic is selected from the group consisting of morphine, codeine, hydromorphone, hydrocodone, oxycodone, oxymorphone, dihydrocodeine, dihydromorphone, and mixtures thereof.

30. A dosage form of claim 29, further comprising a non-opioid drug.
31. The dosage form of claim 30, wherein the said non-opioid drug is a non-steroidal anti-inflammatory agent.
32. The dosage form of claim 31, wherein said non-steroidal anti-inflammatory agent is selected from the group consisting of ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acetaminophen, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam or isoxicam, and mixtures of any of the foregoing.
33. A method for obtaining a bioavailable sustained-release opioid analgesic dosage form for once-a-day oral administration, comprising preparing a plurality



of substrates comprising a unit dose of an oral analgesic in a sustained release form, each of said substrates having a diameter from about 0.1 mm to about 3 mm, said substrates being manufactured to provide an in-vitro dissolution indicative of a once-a-day product.

34. The method of claim 33, wherein said substrates are selected from the group consisting of spheroids, beads, microspheres, seeds, pellets, ion-exchange resin beads, granules, and mixtures thereof.

35. The method of claim 33, further comprising preparing said substrates by coating inert beads with said opioid analgesic, and thereafter overcoating with a hydrophobic material is selected from the group consisting of an acrylic polymer, an alkylcellulose, shellac, zein, hydrogenated vegetable oil, hydrogenated castor oil, and mixtures of any of the foregoing.

36. The method of claim 33, further comprising preparing said substrates as matrices of a substantially uniform mixture of said opioid analgesic and a hydrophobic material.
37. The method of claim 33, further comprising preparing said substrates such that said unit dose provides a peak plasma level of said opioid in-vivo from about 2 to about 10 hours after administration.
38. The method of claim 33, further comprising incorporating said unit dose of said substrates within a hard gelatin capsule.
39. The method of claim 33, further comprising incorporating a therapeutically effective amount of a non-opioid drug into said unit dose.
40. The method of claim 39, wherein the said non-opioid drug is a non-steroidal anti-inflammatory agent.
41. A method of treating a patient for moderate to severe pain with a bioavailable sustained-release opioid analgesic dosage form for once-a-day oral administration, comprising preparing a plurality of

substrates comprising a unit dose of an opioid analgesic, each of said substrates having a diameter from about 0.1 mm to about 3 mm, said substrates being manufactured in a sustained release form to provide therapeutically effective blood levels of said opioid analgesic for about 24 hours or more, and administering said unit dose to a patient to alleviate moderate to severe pain for about 24 hours or more.

42. The method of claim 41, further comprising preparing said substrates in a form selected from the group consisting of spheroids, beads, microspheres, seeds, pellets, ion-exchange resin beads, granules, and mixtures thereof.

43. The method of claim 41, further comprising preparing said substrates by coating inert beads with said opioid analgesic, and thereafter overcoating with a hydrophobic material is selected from the group consisting of an acrylic polymer, an alkylcellulose, shellac, zein, hydrogenated vegetable oil, hydrogenated castor oil, and mixtures of any of the foregoing.

44. The method of claim 41, further comprising preparing said substrates as matrices of a substantially uniform mixture of said opioid analgesic and a hydrophobic material.
45. The method of claim 41, further comprising incorporating a therapeutically effective amount of a non-steroidal anti-inflammatory agent into said unit dose.
46. The method of claim 41, further comprising preparing said substrates such that said unit dose provides a peak plasma level of said opioid in-vivo from about 3 to about 10 hours after administration.
47. The method of claim 41, further comprising preparing said substrates such that said unit dose provides a peak plasma level of said opioid in-vivo from about 2 to about 4 hours after administration.

48. The method of claim 41, further comprising incorporating said unit dose of said opioid analgesic within a hard gelatin capsule.

49. The dosage form of claim 18, wherein said non-opioid drug is selected from the group consisting of acetaminophen and aspirin.

50. The dosage form of claim 30, wherein said non-opioid drug is selected from the group consisting of acetaminophen and aspirin.

51. The method of claim 39, wherein said non-opioid drug is selected from the group consisting of acetaminophen and aspirin.

52. The method of claim 41, further comprising incorporating a therapeutically effective amount of aspirin or acetaminophen into said unit dose.